## REMARKS

Claims 1-17 are pending in the application. Claim 17 has been subjected to a restriction requirement. Claims 11 and 12 have been cancelled by this amendment. Accordingly, claims 1-10 and 13-17 are at issue.

The courteous interview granted by Examiner Ngo to applicant's undersigned attorney on January 14, 1998 is hereby acknowledged with appreciation. During the interview, the Office Action and proposed claim amendments were discussed.

With respect to the Office Action, it was stated that compounds of formula (II) of claim 17 are related to the compounds and process of the claims of elected Group I, and that the compounds of formula (II) would be considered as a part of Group I. Accordingly, applicant has amended claim 17 by deleting the compounds of formulae (III), (V), (VI), (VII), (VIII), and (X). Claim 17, therefore, should be considered on the merits at this time. In addition, claim 16 has been amended to delete processes (B) and (C) from claim 16.

The Office Action indicates that applicant has not filed a certified copy of GB 9401090.7, which applicant relies upon for a claim of foreign priority. However, it is submitted that applicant is not required to submit a certified copy of the priority document in this case.

The present application is the U.S. national phase application of PCT/EP95/00183. Accordingly, it is applicant's understanding that under the procedures of the PCT, a copy of the priority document will have been supplied to the U.S. Patent Office, pursuant to Rule 17 of the PCT regulations. Accordingly, it is requested that the next communication concerning this application

contains an indication that the appropriate priority document is in the file of this application.

The Office Action also requests that a reference to an earlier-filed, and copending, application should be added to the present application. It is submitted that such a reference is not needed because there was *no* previously filed application in the U.S. A PCT application, designating the U.S., was filed on January 19, 1995. Filing of the PCT application in the U.S. was perfected by entering the U.S. national phase on July 17, 1996. Accordingly, no reference to a previously filed and copending application is necessary.

Claims 1-16(A) stand rejected under 35 U.S.C. §112, first and second paragraphs, as being nonenabling or indefinite. In addition, claims 11 and 12 stand rejected under 35 U.S.C. §101. In view of the amendments to the claims, and for the reasons set forth below, it is submitted that these rejections have been overcome and should be withdrawn.

In particular, it is contended that the phrase "$R^1$ and $R^3$ together represent . . . alkyl or alkenyl chain" is not clear. As indicated in the Office Action, this phrase is intended to recite that $R^1$ and $R^3$ are taken together to form a ring. Accordingly, claim 1 has been amended to recite that $R^1$ and $R^3$ are taken together as a component of a 5- or 6-membered ring. $R^1$ and $R^3$, together, contribute three or four members of the ring, and the remaining two members are the nitrogen atom bonded to $R^1$ and the carbon atom bonded to $R^3$.

From a reading of all substituents $R^1$ and $R^3$ recited in claim 1, the phrase in question can only be construed as taking $R^1$ and $R^3$ together to form a ring. For example, $R^1$ can be $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, or $C_{2-6}$ alkynyl (and others), and $R^3$ can be hydrogen or $C_{1-3}$ alkyl.

Based on those definitions of $R^1$ and $R^3$, the only reasonable construction of taking $R^1$ and $R^3$ together is to form a ring. Any other construction would be redundant in view of the recited definitions of $R^1$ and $R^3$. It is submitted, therefore, that the amendment to claim 1 overcomes this rejection under 35 U.S.C. §112, second paragraph.

The phrase "and salts and solvates" also is considered indefinite. Accordingly, applicant has amended claims 1, 2, 8, 9, and 10 to recite "or salts or solvates." This amendment clarifies that there are not multiple forms of the compound of formula (I) in one compound. It again is submitted that these amendments to claims 1, 2, 8, 9 and 10 overcome this rejection under 35 U.S.C. §112, second paragraph.

Claims 11 and 12 stand rejected under 35 U.S.C. §112, second paragraph, and 35 U.S.C. §101. In view of this amendment, which cancels claims 11 and 12, it is submitted that these rejections are now moot.

Claims 1-16(A) stand rejected under 35 U.S.C. §112, first paragraph, as not being enabling for a compound of formula (I) when $R^1$ and $R^3$ are taken together form a chain, because such a compound cannot be synthesized. It is submitted that this contention is incorrect, and, for the reasons set forth below, this rejection should be withdrawn.

As stated above, when $R^1$ and $R^3$ are taken together, these substituents form a ring. To illustrate how a compound of formula (I) can be made when $R^1$ and $R^3$ are taken together to form a ring, the examiner's attention is directed to compound (IX) at page 13 of the specification. As stated in the specification,

"There is further provided by the present invention a process (B) for preparing a compound of formula (I), wherein $R^1$ and $R^3$ together represent a 3- or 4-membered alkyl or alkenyl chain, which process (B) comprises cyclisation of a compound of formula (VIII)" (page 13, lines 3-6), and

"Conveniently a compound of formula (VIII) is prepared by reaction of a compound of formula (III) as hereinbefore described with a compound of formula (IX)" (page 13, lines 13-15).

The compound of formula (III) is illustrated in the specification at the top of page 10.

Therefore, to prepare a compound of formula (I) wherein $R^1$ and $R^3$ are taken together to form a ring, the following reaction sequence is used.

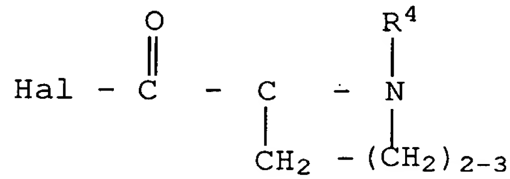
$$(III) + (IX) \longrightarrow (VIII) \xrightarrow{\text{cyclization}} (I)$$

The compound of formula (III) is disclosed at page 10 of the specification. The cyclization step is disclosed at page 13, lines 8-12.

The synthesis of a compound of formula (I), wherein $R^1$ and $R^3$ are taken together to form a ring, therefore, can be accomplished by providing a compound of formula (IX), wherein $R^1$ and $R_3$ are taken together to form a ring. In particular, a compound of formula (IX) has the following structure.

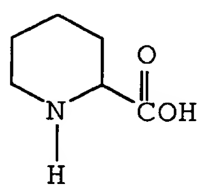
```
        O   R4
        ||  |
   Hal-C-C-N-R1
          |
          R3
```

A compound of formula (IX) having $R^1$ and $R^3$ taken together to form a 5- or 6-membered ring could have the structure

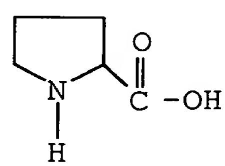


wherein Hal represent a halogen atom, like chlorine (see specification, page 9, lines 26-27), and $R^4$ is a protecting group, like benzyloxycarbonyl (see specification, page 13, lines 17-18). Synthesis of the above compound would provide a compound of formula (IX), which in turn could be used to prepare a compound of formula (I) by the above reaction sequence.

The above compound can be prepared from compounds and synthetic steps well known to persons skilled in the art. For example, a suitable starting material would be picolinic acid or proline, having the following structures (a) and (b), respectively.



(a)

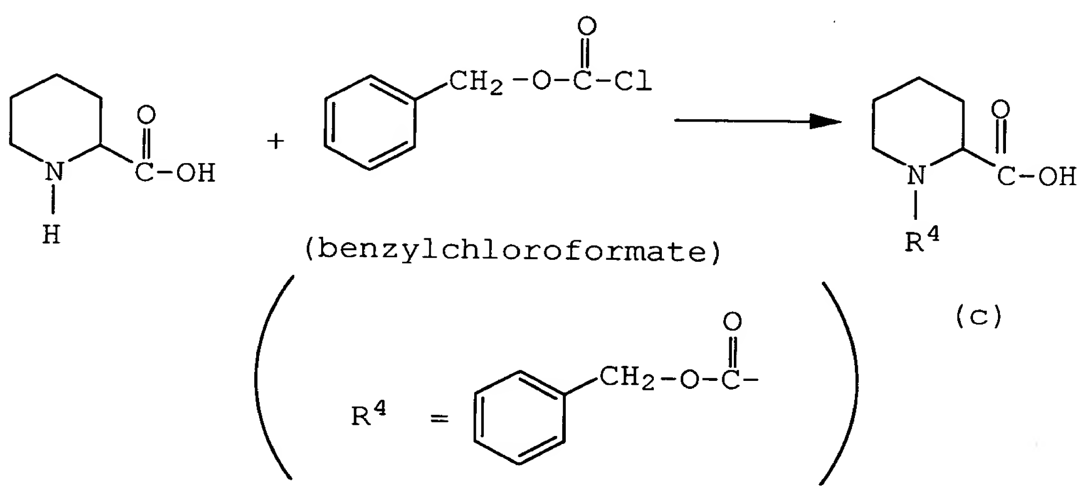


(b)

These compounds are available commercially, as illustrated in pages 1019 and 1057, of the 1992 catalog of

Aldrich Chemical Co., Milwaukee, WI, attached hereto as Exhibit A. In these starting materials, $R^1$ and $R^3$ are taken together to form a 4-membered alkyl chain and a 3-membered alkyl chain, respectively, as a component of a 6-membered ring and a 5-membered ring, respectively.

Compound (a) or (b) then can be reacted with a protecting compound, like benzylchloroformate, to position a protecting group, like benzyloxycarbonyl, on the nitrogen atom. This reaction is illustrated in C.D. Gutsche et al., "Fundamentals of Organic Chemistry," Prentice-Hall, Inc., Englewood Cliffs, NJ, page 1190, attached hereto as Exhibit B. This reaction is illustrated below for compound (a) and an identical reaction can be performed on compound (b).

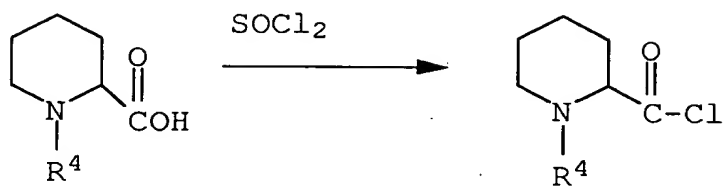



(c)

Benzylchloroformate is available commercially, as illustrated at page 132 of Exhibit A.

Compound (c) then can be reacted with a common reagent for converting a carboxylic acid to an acid chloride, like thionyl chloride ($SOCl_2$), to provide com-

pound (d). This reaction is illustrated at page 39 of Exhibit B.




(c) (d)

Compound (d) corresponds to the compound of formula (IX) at page 13 of the specification, wherein Hal is chlorine, $R^4$ is benzyloxycarbonyl, and $R^1$ and $R^3$ are taken together as a 4-membered alkyl chain component of a 6-membered ring. An identical reaction sequence starting with proline would yield an identical compound of formula (IX), except $R^1$ and $R^3$ are taken together as a 3-membered alkyl component of a 5-membered ring.

Compound (d), or a similar compound prepared from proline, then could be reacted with a compound of formula (III) to yield a compound of formula (VIII), which in turn is cyclized to form a compound of formula (I).

Therefore, a compound of formula (I) can be prepared when $R^1$ and $R^3$ are taken together as a 3- or 4-membered alkyl or alkenyl chain. The synthesis utilizes well-known starting materials, reagents, and reactions. Accordingly, it is submitted that the rejection of claims 1-16(A) under 35 U.S.C. §112, first paragraph, should be withdrawn.

During the interview, the examiner stated that the claims appeared excessive in scope because of the terms aryl and heteroaryl. In response, applicant has

amended claim 1 to more particularly claim the aryl and heteroaryl substituents. Support for this amendment can be found in the specification at page 2, lines 16-17.

It is submitted that the claims are now in proper form and scope for allowance. Early and favorable action on the merits are respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

**MARSHALL, O'TOOLE, GERSTEIN, MURRAY & BORUN**

By James J. Napoli

James J. Napoli
(Registration No. 32,361)
Attorneys for Applicant
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
(312) 474-6300

Chicago, Illinois
February 6, 1998

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Exhibit A

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**Benzylbis(triphenylphosphine)palladium(II) chloride**, see 27,766-5, *trans*-Benzyl(chloro)bis(triphenylphosphine)palladium(II) *page 132*

B1,790-5 ★ **Benzyl bromide**, 98% *[100-39-0]* (α-bromotoluene) $C_6H_5CH_2Br$ FW 171.04 mp -3 to -1° bp 198-199° $n_D^{20}$ 1.5750 d 1.438 Fp 188°F(86°C) *Beil.* 5,306 *Fieser* 5,25 *Merck Index* 11,1142 *NMR* 2(1),774D *FT-IR* 1(3),890B *Safety* 2,381B *RTECS#* XS7965000 Disp. C *CORROSIVE LACHRYMATOR* ........ 25g 9.40; 100g 23.80; 500g 77.95

24,563-1 **Benzyl 2-bromoacetate**, 96% *[5437-45-6]* $BrCH_2CO_2CH_2C_6H_5$ FW 229.08 bp 166-170°/22mm $n_D^{20}$ 1.5440 d 1.446 Fp >230°F(110°C) *Beil.* 6(1),220 *NMR* 2(2),269B *FT-IR* 1(3),1336D *Safety* 2,381C *RTECS#* AF5957215 Disp. A *IRRITANT* ........ 50g 15.00; 250g 48.60

38,204-3 NEW **Benzyl 3-bromopropyl ether** *[54314-84-0]* $C_6H_5CH_2O(CH_2)_3Br$ FW 229.12 Disp. A *IRRITANT* ........ 1g 9.00; 10g 62.00

**Benzyl-*tert*-butanol**, see B1,800-6, α,α-Dimethylbenzenepropanol *page 492*

30,850-1 ★ **Benzyl butyl phthalate**, 98% *[85-68-7]* $2\text{-}[CH_3(CH_2)_3O_2C]C_6H_4CO_2CH_2C_6H_5$ FW 312.37 $n_D^{20}$ 1.5400 d 1.100 Fp >230°F(110°C) *Beil.* 9(2),594 *FT-IR* 1(3),1377A *Safety* 2,381D *RTECS#* TH9990000 Disp. A *IRRITANT* ........ 5ml 10.00; 250ml 14.60; 1L 40.60

B1,820-0 **Benzyl carbamate**, 99% *[621-84-1]* $H_2NCO_2CH_2C_6H_5$ FW 151.17 mp 87-89° *Beil.* 6,437 *NMR* 2(2),361A *FT-IR* 1(2),389D Disp. A ........ 25g 21.20; 100g 51.05

12,101-0 ***S*-Benzyl-*N*-carbobenzyloxy-L-cysteine**, 98% *[3257-18-9]* $C_6H_5CH_2SCH_2CH(NHCO_2CH_2C_6H_5)CO_2H$ FW 345.42 mp 94-96° $[\alpha]^{23}$ -44° (c = 2, $C_2H_5OH$) *NMR* 2(2),264C *FT-IR* 1(2),265D Disp. A ........ 10g 13.05; 25g 27.95

**1-Benzyl-3-carbomethoxy-4-piperidone hydrochloride**, see 22,700-5, Methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride *page 826*

22,900-8 ★ **Benzylcetyldimethylammonium chloride monohydrate** $C_6H_5CH_2N[(CH_2)_{15}CH_3](CH_3)_2Cl\cdot H_2O$ FW 414.12 mp 62-64° *Beil.* 12(3),2212 *Merck Index* 11,2009 *NMR* 2(1),1122B *FT-IR* 1(1),1321C *Safety* 2,382A *RTECS#* BO6822450 Disp. A *CORROSIVE* ........ 5g 8.80; 25g 13.20; 100g 38.70

28,847-0 **Benzyl-α-$^{13}$C chloride**, 99 atom % $^{13}$C *[57742-41-3]* (α-chlorotoluene-α-$^{13}$C) $C_6H_5{}^{13}CH_2Cl$ FW 127.58 mp -43° bp 177-181° $n_D^{20}$ 1.5380 d 1.100 Fp 165°F(73°C) *Safety* 2,382C Disp. C *HIGHLY TOXIC CANCER SUSPECT AGENT* (*Packaged in prescored ampules*) ........ 250mg 164.10; 1g 455.80

21,733-6 **Benzyl-*d*$_7$ chloride**, 99+ atom % D *[59502-05-5]* (α-chlorotoluene-$d_7$) $C_6D_5CD_2Cl$ FW 133.64 bp 65°/10mm $n_D^{20}$ 1.5374 d 1.200 Fp 165°F(73°C) *NMR* 2(1),6C *FT-IR* 1(3),1616C *Safety* 2,383A Disp. C *HIGHLY TOXIC CANCER SUSPECT AGENT* ........ 1g 82.60

18,555-8 ★ **Benzyl chloride**, 99% *[100-44-7]* (α-chlorotoluene) $C_6H_5CH_2Cl$ FW 126.59 mp -43° bp 177-181° $n_D^{20}$ 1.5380 d 1.100 Fp 165°F(73°C) *Beil.* 5,292 *Merck Index* 11,1143 *NMR* 2(1),774C *FT-IR* 1(3),890A *Safety* 2,382B *RTECS#* XS8925000 Disp. C *HIGHLY TOXIC CANCER SUSPECT AGENT* Mutagen, possible carcinogen. *Proc. Nat. Acad. Sci. U.S.*, 72, 979 (1975). Inhibited with 0.25% propylene oxide ........ 50g 10.00; 250g 12.90; 1kg 17.90; 4kg† 48.20

32,016-1 ★ **Benzyl chloride**, 97% *[100-44-7]* (α-chlorotoluene) $C_6H_5CH_2Cl$ Inhibited with 0.25% propylene oxide (*Packaged in poly-coated bottle*) ........ 1L 21.20

13,359-0 ★ **Benzyl chloride** *[100-44-7]* (α-chlorotoluene) $C_6H_5CH_2Cl$ Inhibited with 0.25% propylene oxide ........ 100g 11.90; 1kg 17.40; 4kg† 46.30

27,766-5 ***trans*-Benzyl(chloro)bis(triphenylphosphine)palladium(II)** *[22784-59-4]* [benzylbis(triphenylphosphine)palladium(II) chloride] $[(C_6H_5)_3P]_2Pd(CH_2C_6H_5)Cl$ FW 757.58 mp 166-170° *Fieser* 8,35 9,41 10,26 12,44 13,30 *Safety* 2,383C Disp. R *IRRITANT* ........ 100mg 19.30; 500mg 63.40

Catalyst for the coupling of alkyl-,[1] vinyl-[2] or alkynyltin[3] groups with acyl chlorides. 1. *J. Am. Chem. Soc.*, 100, 3636 (1978). 2. *Tetrahedron Lett.*, 24, 2361 (1983). 3. *J. Org. Chem.*, 47, 2549 (1982). See also, *Aldrichimica Acta.*, 17(3), 75 (1984).

11,993-8 ★ **Benzyl chloroformate**, tech., 95% *[501-53-1]* (carbobenzoxy chloride) $ClCO_2CH_2C_6H_5$ FW 170.60 $n_D^{20}$ 1.5190 d 1.195 Fp 197°F(91°C) *Beil.* 6,437 *Fieser* 1,109 2,59 15,22 *Merck Index* 11,1807 *NMR* 2(2),331D *FT-IR* 1(2),353C *Safety* 2,383D *RTECS#* LQ5860000 Disp. A *HIGHLY TOXIC CANCER SUSPECT AGENT* Protecting reagent in peptide synthesis. May contain ≤3% benzyl chloride ........ 5g 11.90; 100g 28.40; 5x100g 86.10

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35,958-0 (8*S*,9*R*)-(-)-*N*-Benzylcinchonidi
mp 210° (dec.) $[\alpha]_D^{20}$ -180° (c =

36,618-8 NEW *N*-Benzylcinchoninium chlori
*Beil.* 23,436 *Fieser* 12,380
Remainder *N*-benzyldihydrocinc

23,421-4 ★ **Benzyl cinnamate**, 99% *[103-*
mp 37-39° bp 195-200°/5mm
*Index* 11,1144 *NMR* 2(2),276C

18,572-8 ★ **Benzyl cyanide**, 99+ % *[140-2*
mp -24° bp 233-234° $n_D^{20}$ 1.5
*Index* 11,1145 *NMR* 2(2),395A
*RTECS#* AM1400000 Disp. A

B1,940-1 ★ **Benzyl cyanide**, 98% *[140-29-4*

32,058-7 **Benzyl cyanoformate**, 97% *[55*
bp 66-67°/0.6mm $n_D^{20}$ 1.5046
*Safety* 2,384D Disp. A *HIGHL*

18,717-8 **1-Benzyl-4-cyano-4-hydroxypipe**
(1-benzyl-4-hydroxyisonipeco
*FT-IR* 1(2),438D *Safety* 2,385A

27,798-3 ***N*-Benzylcyclopropanecarboxar**
FW 175.23 mp 142-144° Disp.

B1,980-0 ★ ***S*-Benzyl-L-cysteine**, 97% *[3054*
mp 214° (dec.) $[\alpha]_D^{20}$ -10° (c = 2, 1
*FT-IR* 1(2),251C Disp. A

85,866-8 ★ ***S*-Benzyl-L-cysteine-4-nitroanilid**
$C_6H_5CH_2SCH_2CH(NH_2)CONHC_6H_4N$
$[\alpha]_D^{20}$ -68.6° (c = 0.5, dioxane) *FT-IF*
Substrate for cystine aminopeptid

34,525-3 ***S*-Benzyl-L-cysteinol**, 97% *[8824*
$C_6H_5CH_2SCH_2CH(NH_2)CH_2OH$ FW
$[\alpha]_D^{20}$ -49° (c = 1.4, $C_2H_5OH$) *Beil.* 6

15,544-6 **Benzyl diethyl phosphite** *[2768-3*
bp 110°/2mm $n_D^{20}$ 1.4930 d 1.07
*FT-IR* 1(2),552A *Safety* 2,385D

34,853-8 ★ **Benzyldiethyl(2,6-xylylcarbamoyl**
*[3734-33-6]* (denatonium benzo
$C_6H_5CH_2N(C_2H_5)_2CH_2CONHC_6H_3(CH_3$
*Index* 11,2877 *RTECS#* BO665000

**Benzyldimethylamine**, see *N*,*N*-Di

36,822-9 NEW **Benzyl *N*,*N*-dimethyldithiocarbam**
FW 211.35 mp 39-41° Fp >230

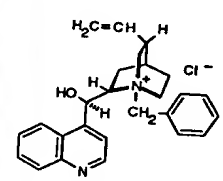
28,088-7 ★ **Benzyldimethyldodecylammonium**
$C_6H_5CH_2N[(CH_2)_{11}CH_3](CH_3)_2Br$ FW
*Fieser* 7,16 *Safety* 2,386A *RTEC*
Contains ~3% water

12,719-1 ★ ***N'*-Benzyl-*N*,*N*-dimethylethylenedi**
$C_6H_5CH_2NHCH_2CH_2N(CH_3)_2$ FW 178
Fp >230°F(110°C) *NMR* 2(1),1071C
*IRRITANT*

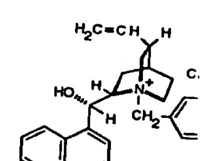
34,899-6 **2'-Benzyl-2,2-dimethylpropionanilid**
$(CH_3)_3CCONHC_6H_4CH_2C_6H_5$ FW 267.
Reagent for the titration of organolith

***N*-Benzyl-*N'*,*N'*-dimethyl-*N*-(2-pyridy**
28,738-5, Tripelennamine hydrocl

86,203-7 **Benzyl *S*-(4,6-dimethylpyrimidin-2-yl**
FW 274.34 mp 64-66° Disp. A
$NH_2$-protecting reagent for amino acid
*Chem. Eng. News*, 54(22), 3 (1976). *Ibid*

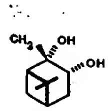



35,958-0




36,618-8

| | | | $ |
|---|---|---|---|
| 28,236-7 | **(1S,2S,3R,5S)-(+)-Pinanediol, 99%** [*18680-27-8*] {[1S-(1α,2α,3α,5α)]-2,6,6-trimethylbicyclo[3.1.1]heptane-2,3-diol} FW 170.25 mp 57-59° Fp >230°F(110°C) [α]D +8.5° (c=6.5, $C_6H_5CH_3$) *Beil.* 6(3),4145 *FT-IR* 1(3),250D Disp. A<br>Chiral reagent in the synthesis of (2S,3S)- and (2R,3S)-3-phenyl-2-butanol. *J. Am. Chem. Soc.*, 102, 7590 (1980). | 1g<br>5g | 13.70<br>45.60 |
| | **3-Pinanol**, see Isopinocampheol | | |
| 28,410-6 | **Pindolol, 97%** [*13523-86-9*] {1-(1H-indol-4-yloxy)-3-[(1-methylethyl)amino]-2-propanol} FW 248.33 mp 167-171° *Merck Index* 11,7412 *Safety* 2,2840C *RTECS#* UB6660000 Disp. A *TOXIC IRRITANT* | 250mg<br>1g | 11.80<br>26.90 |
| …07-0 ★ | **(1R)-(+)-α-Pinene, 99+%** [*7785-70-8*] FW 136.24 mp -62° bp 155-156° nD 1.4660 d 0.857 Fp 90°F(32°C) [α][21] +50.7° (neat) *Beil.* 5,146 *Merck Index* 11,7414 *Safety* 2,2841A Disp. D *FLAMMABLE LIQUID IRRITANT*<br>Precursor to monoisopinocampheylborane ($IPCBH_2$) used to prepare (+)-*trans*-2-methylcyclohexanol from 1-methylcyclohexene in 72.4% e.e. *J. Am. Chem. Soc.*, 99, 5514 (1977). Chiral intermediate. *Aldrichimica Acta*, 13(1), 13 (1980). *Ibid.*, 20(1), 24 (1987).<br>98+% e.e. | 5g<br>25g | 17.00<br>55.40 |
| P4,568-0 ★ | **(1R)-(+)-α-Pinene, 98%** [*7785-70-8*] [α][22] +47.1° (neat)<br>91+% e.e. | 100ml<br>500ml | 22.40<br>77.00 |
| …45-1 ★ | **(1R)-(+)-α-Pinene, tech., 85%** [*7785-70-8*] [α]D +43° (neat) | 100ml<br>500ml | 15.20<br>48.40 |
| …762-4 | **(±)-α-Pinene, 98%** [*2437-95-8*] FW 136.24 bp 155-156° nD 1.4650 d 0.858 Fp 90°F(32°C) *Beil.* 5,144 *Merck Index* 11,7414 *NMR* 2(1),52D *FT-IR* 1(3),75B *Safety* 2,2840D Disp. D *FLAMMABLE LIQUID IRRITANT* | 5ml<br>250ml<br>1L | 11.90<br>22.80<br>62.20 |
| …0,571-5 ★ | **(1S)-(-)-α-Pinene, 99%** [*7785-26-4*] FW 136.24 bp 155-156° nD 1.4650 d 0.855 Fp 90°F(32°C) [α]D -50.7° (neat) *Beil.* 5,144 *Merck Index* 11,7414 *Safety* 2,2841B Disp. D *FLAMMABLE LIQUID IRRITANT*<br>98+% e.e. | 5g<br>25g | 17.40<br>58.50 |
| …,439-9 ★ | **(1S)-(-)-α-Pinene, 99+%** [*7785-26-4*] [α]D -45° (neat)<br>87+% e.e. | 25g<br>100g | 12.70<br>32.60 |
| P4,570-2 ★ | **(1S)-(-)-α-Pinene, 98%** [*7785-26-4*] [α][22] -42° (neat)<br>81+% e.e. | 100ml<br>500ml | 9.95<br>29.85 |
| 11,208-9 ★ | **(1S)-(-)-β-Pinene, 99%** [*18172-67-3*] FW 136.24 mp -61° bp 165-167° nD 1.4780 d 0.859 Fp 91°F(32°C) [α]D -21° (neat) *Beil.* 5,154 *Merck Index* 11,7415 *NMR* 2(1),54A *FT-IR* 1(3),75D *Safety* 2,2841C *RTECS#* DT5077000 Disp. D *FLAMMABLE LIQUID IRRITANT*<br>Chiral intermediate. *Aldrichimica Acta*, 13(1), 13 (1980). | 5ml<br>250ml<br>1L<br>4L | 11.90<br>18.30<br>56.40<br>97.85 |
| 21,830-8 ★ | **α-Pinene oxide, 98%** [*1686-14-2*] FW 152.24 bp 102-103°/50mm nD 1.4690 d 0.964 Fp 150°F(65°C) [α][20] -81° (neat) *Beil.* 5,152 *NMR* 2(1),198D *FT-IR* 1(3),312D *Safety* 2,2841D *RTECS#* RP5600000 Disp. C | 50g<br>250g | 18.50<br>60.00 |
| 21,831-6 ★ | **β-Pinene oxide, 90%** [*6931-54-0*] FW 152.24 bp 98-100°/27mm nD 1.4770 d 0.976 Fp 151°F(66°C) [α]D +7° (neat) *Beil.* 17(2),44 *NMR* 2(1),199A *FT-IR* 1(1),237B *Safety* 2,2842A *RTECS#* TK4570000 Disp. C | 50g | 26.00 |
| 11,010-8 | ***cis*-Pinonic acid, 98%** [*473-72-3*] (*cis*-3-acetyl-2,2-dimethylcyclobutaneacetic acid) $CH_3COC_4H_4(CH_3)_2CH_2CO_2H$ FW 184.24 mp 104-107° *Beil.* 10,622 *NMR* 2(1),469D *FT-IR* 1(1),533A *Safety* 2,2842B Disp. C *IRRITANT* | 5g<br>25g | 22.45<br>73.10 |
| | **Pipecolic acid**, see P4585-0, Pipecolinic acid *page 1019* | | |
| | **Pipecoline**, see Methylpiperidine | | |
| 28,806-2 | **D-Pipecolinic acid, 99%** [*1723-00-8*] [(R)-(+)-2-piperidinecarboxylic acid] FW 129.16 mp 277° (dec.) [α][25] +27° (c=1, $H_2O$) *Beil.* 22,8 *Merck Index* 11,7425 *Safety* 2,2842D Disp. A *IRRITANT* | 25mg<br>100mg | 22.10<br>59.85 |
| P4,585-0 | **DL-Pipecolinic acid, 98%** [*4043-87-2*] (2-piperidinecarboxylic acid) FW 129.16 mp 282° (dec.) *Beil.* 22,7 *Merck Index* 11,7425 *NMR* 2(1),505C *FT-IR* 1(1),585B *Safety* 2,2843A *RTECS#* TK6021000 Disp. A *IRRITANT* | 25g<br>100g | 41.30<br>112.00 |
| 24,852-5 | **DL-Pipecolinic acid hydrochloride, 99%** [*5107-10-8*] (2-piperidinecarboxylic acid) FW 165.62 mp 263-266° *Beil.* 22,7 *Merck Index* 11,7425 *FT-IR* 1(1),585C *Safety* 2,2843B Disp. A *IRRITANT HYGROSCOPIC* | 5g | 28.95 |
| 23,775-2 | **L-Pipecolinic acid, 99%** [*3105-95-1*] [(S)-(-)-2-piperidinecarboxylic acid] FW 129.16 mp 272° [α][25] -26.4° (c=1, $H_2O$) *Beil.* 22,8 *Merck Index* 11,7425 *NMR* 2(1),505D *FT-IR* 1(1),585D *Safety* 2,2842C Disp. A *IRRITANT*<br>Proline homolog. Occurs in seeds, malt, edible mushrooms, fruits, etc. | 100mg | 23.60 |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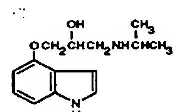
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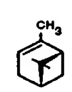
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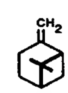
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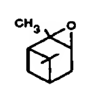
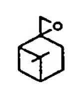

21,830-8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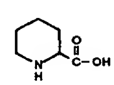
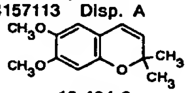

P4,585-0

| | | | $ |
|---|---|---|---|
| 22,702-4 | **5β-Pregnane-3α,17α,20α-triol**, 98% [1098-45-9] FW 338.52 mp 250-252° $[\alpha]^{25}_{D}$ -3.5° (c = 0.5, $C_2H_5OH$) *Beil.* 6(3),6405 *Safety* 2,2926D Disp. A | 25mg<br>100mg | 12.40<br>31.90 |
| 14,766-4 | **Pregnenolone**, 98% [145-13-1] FW 316.49 mp 190-192° $[\alpha]^{23}_{D}$ +27° (c = 1, $C_2H_5OH$) *Merck Index* 11,7739 *NMR* 2(2),923A *FT-IR* 1(2),1051D *Safety* 2,2940C *RTECS#* TU5560700 Disp. A | 5g<br>25g | 11.20<br>35.60 |
| 21,990-2 | **Pregnenolone acetate**, 99% [1778-02-5] FW 358.52 mp 149-152° $[\alpha]^{25}_{D}$ +19° (c = 1, $C_2H_5OH$) *Merck Index* 11,7739 *NMR* 2(2),936D *FT-IR* 1(2),1061C *Safety* 2,2940D Disp. A | 5g<br>25g | 9.45<br>33.30 |
| | **Prehnitene**, see 15,360-5, 1,2,3,4-Tetramethylbenzene *page 1171* | | |
| | **Prenyl bromide**, see 24,990-4 4-Bromo-2-methyl-2-butene *page 198* | | |
| | **Pr(fod)₃**, see 16,135-7, Resolve-Al PrFOD® *page 1088* | | |
| | **Pr(hfc)₃**, see Tris[3-(heptafluoropropylhydroxymethylene)camphorato], praseodymium(III) derivative | | |
| 16,039-3 | **Primaquine diphosphate**, 99% [63-45-6] [8-(4-amino-1-methylbutylamino)-6-methoxyquinoline] FW 455.35 mp 205-206° (dec.) *Merck Index* 11,7751 *NMR* 2(2),741A *FT-IR* 1(2),864B *Safety* 2,2942C *RTECS#* VA9660000 Disp. A *TOXIC* | 1g<br>10g | 7.10<br>35.55 |
| 20,686-5 | **Primuline** [8064-60-6] (C.I. 49000, Direct Yellow 59) FW 475.55 λmax 356nm *FT-IR* 1(2),1039B *UV-Vis* 588 *RTECS#* TV1050000 Disp. A<br>Useful in a simple retrograde double-labeling procedure for studying axonal branching, in combination with 4′,6-diamidino-2-phenylindole dihydrochloride (DAPI, 21,708-5) and Evans Blue (20,633-4). *Science*, **204**, 873 (1979).<br>Dye content ~75% | 25g<br>100g | 13.60<br>42.10 |
| | **Pristane**, see T2280-2, 2,6,10,14-Tetramethylpentadecane *page 1175* | | |
| 22,296-8 ★ | **Procainamide hydrochloride**, 99% [614-39-1] [4-amino-N-(2-diethylaminoethyl)benzamide] $H_2NC_6H_4CONHCH_2CH_2N(C_2H_5)_2\cdot HCl$ FW 271.79 mp 167-169° *Beil.* 14(3),1077 *Merck Index* 11,7762 *NMR* 2(2),350C *FT-IR* 1(2),373B *Safety* 2,2942D *RTECS#* CV2295000 Disp. A *IRRITANT* | 25g | 8.80 |
| 24,303-5 | **Procaine**, 99+% [59-46-1] [2-(diethylamino)ethyl 4-aminobenzoate] $H_2NC_6H_4CO_2CH_2CH_2N(C_2H_5)_2$ FW 236.32 mp 61-62° *Beil.* 14,424 *Merck Index* 11,7763 *NMR* 2(2),288B *FT-IR* 1(2),303C *Safety* 2,2943A *RTECS#* DG2100000 Disp. A *TOXIC IRRITANT* | 25g<br>100g | 11.90<br>31.60 |
| 22,297-6 ★ | **Procaine hydrochloride**, 99% [51-05-8] [2-(diethylamino)ethyl 4-aminobenzoate] $H_2NC_6H_4CO_2CH_2CH_2N(C_2H_5)_2\cdot HCl$ FW 272.78 mp 155-156° *Beil.* 14,424 *NMR* 2(2),349D *FT-IR* 1(2),303D *Safety* 2,2943B *RTECS#* DG2275000 Disp. A *TOXIC IRRITANT* | 5g<br>100g | 8.10<br>14.85 |
| | **Procion Blue HB**, see 24,222-5, Reactive Blue 2 *page 1085* | | |
| 37,255-2 | **Procion Yellow H-E3G** [59112-78-6] (Reactive Yellow 81) Disp. A | 10g<br>50g | 10.00<br>33.50 |
| | **Proflavine hemisulfate**, see 19,822-6, 3,6-Diaminoacridine hemisulfate *page 381* | | |
| | **Proflavine hydrochloride**, see 13,110-5, 3,6-Diaminoacridine hydrochloride *page 381* | | |
| 85,045-4 ★ | **Progesterone**, 98% [57-83-0] FW 314.47 mp 129-130° $[\alpha]^{23}_{D}$ +182° (c = 2, dioxane) *Merck Index* 11,7783 *FT-IR* 1(2),1052B *Safety* 2,2944C *RTECS#* TW0175000 Disp. A *CANCER SUSPECT AGENT MUTAGEN* | 5g<br>25g | 9.30<br>36.20 |
| 28,705-9 | **L-Prolinamide**, 98% [7531-52-4] FW 114.15 mp 95-97° $[\alpha]^{20}_{D}$ -100° (c = 2, $C_2H_5OH$) *Beil.* 22(3),15 Disp. A | 250mg<br>1g | 11.80<br>31.80 |
| 85,891-9 ★ | **D-Proline**, 99+% [344-25-2] [(R)-(+)-proline] FW 115.13 mp 223° (dec.) $[\alpha]^{22}_{D}$ +85.0° (c = 4, $H_2O$) *Beil.* 22,2 *Fieser* 7,307 9,393 *FT-IR* 1(1),583B *Safety* 2,2946D Disp. A | 100mg<br>500mg<br>5g | 6.30<br>17.90<br>77.10 |
| 17,182-4 ★ | **DL-Proline**, 99% [609-36-9] FW 115.13 mp 208° (dec.) *Beil.* 22,4 *Fieser* 9,393 *Merck Index* 11,7790 *NMR* 2(1),504A *FT-IR* 1(1),583A *Safety* 2,2946C Disp. A | 1g<br>5g | 6.40<br>19.85 |
| 13,154-7 ★ | **L-Proline**, 99+% [147-85-3] [(S)-(-)-proline] FW 115.13 mp 228° (dec.) $[\alpha]^{20}_{D}$ -84° (c = 4, $H_2O$) *Beil.* 22,2 *Fieser* 6,492 8,421 9,393 10,331 12,414 *Merck Index* 11,7790 *FT-IR* 1(1),583C *Safety* 2,2946A *RTECS#* TW3584000 Disp. A<br>Optically active intermediate for organic synthesis. *Aldrichimica Acta*, **13**(1), 13 (1980). | 2.5g<br>25g<br>100g | 5.90<br>10.55<br>33.50 |



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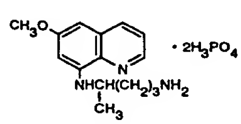

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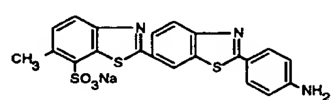

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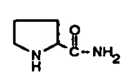

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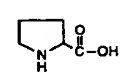

13,154-7

Exhibit B


*C. David Gutsche*
*Department of Chemistry*
*Washington University, St. Louis*

*Daniel J. Pasto*
*Department of Chemistry*
*University of Notre Dame*


# *Fundamentals of Organic Chemistry*

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Acid halides are distinguished from the corresponding acids by a carbonyl stretching band at a significantly higher frequency in the infrared. Whereas type AC carboxylic acids absorb at 1725–1700 $cm^{-1}$, the corresponding acid chlorides absorb at 1815–1770 $cm^{-1}$ (see Table 15.2 on p. 394).

15.1c. SYNTHESIS OF ACID HALIDES. Acid halides are almost invariably synthesized from the corresponding carboxylic acids by the action of any one of several inorganic reagents, including phosphorus trichloride ($PCl_3$), phosphorus pentachloride ($PCl_5$), and thionyl chloride ($SOCl_2$) (Fig. 15.1).

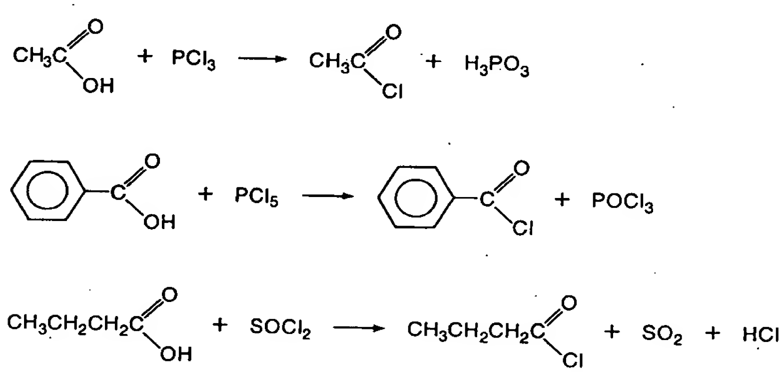
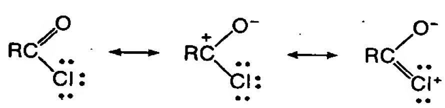


**Fig. 15.1.** Synthesis of acid chlorides from carboxylic acids.

15.1d. REACTIONS OF ACID HALIDES. We might predict that the electrophilic character of the carbonyl carbon in acid halides should be greater than in aldehydes and ketones because of the electron-withdrawing effect (*i.e.*, inductive effect) of the halogen atom. This does, in fact, prove to be the case, although to some extent this effect is counterbalanced by the electron-releasing effect of the nonbonded electrons of the halogen [*e.g.*, resonance structure Fig. 15.2(c)];

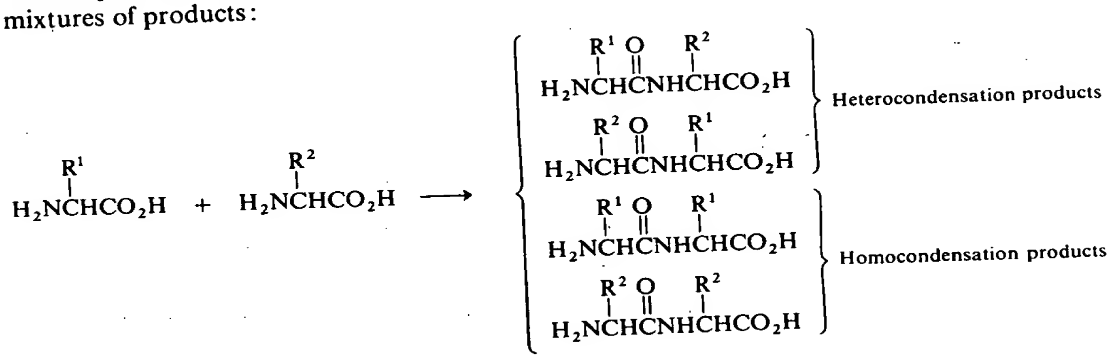


(a) (b) (c)

**Fig. 15.2.** Resonance structures of acid chlorides.

acid halides are exceedingly reactive toward nucleophilic reagents. The products of reaction, however, are different from those from aldehydes and ketones (see Section 13.5), for the initial step, producing an addition product, is succeeded by a second step, in which the halogen is eliminated and the carbonyl group is regenerated. The overall reaction is a *substitution* process, which proceeds via nucleophilic addition followed by elimination. The hydrolysis of acetyl chloride, for instance, can be depicted in this fashion (Fig. 15.3).

First, amino acids are bifunctional molecules capable of undergoing facile reaction at the carboxyl function as well as the amino function. Thus, if we wish to form a peptide link between two *different* amino acids, we immediately face the problem associated with any mixed condensation—*viz.*, the formation of mixtures of products:




To circumvent this problem, we must "protect" or "block" the amino group of one of the participants and the carboxyl group of the other. Amino groups are frequently protected by means of the *t*-butoxycarbonyl (*t*-BOC) function, prepared by the action of *t*-butyl azidoformate [$(CH_3)_3COCON_3$] or *t*-butyl chloroformate [$(CH_3)_3COCOCl$] on the amino acid. Carboxyl groups can be protected by conversion to the benzyl or *t*-butyl ester. All of these are good protecting groups because they are easily removed under mild acid-catalyzed hydrolysis (Fig. 39.9).

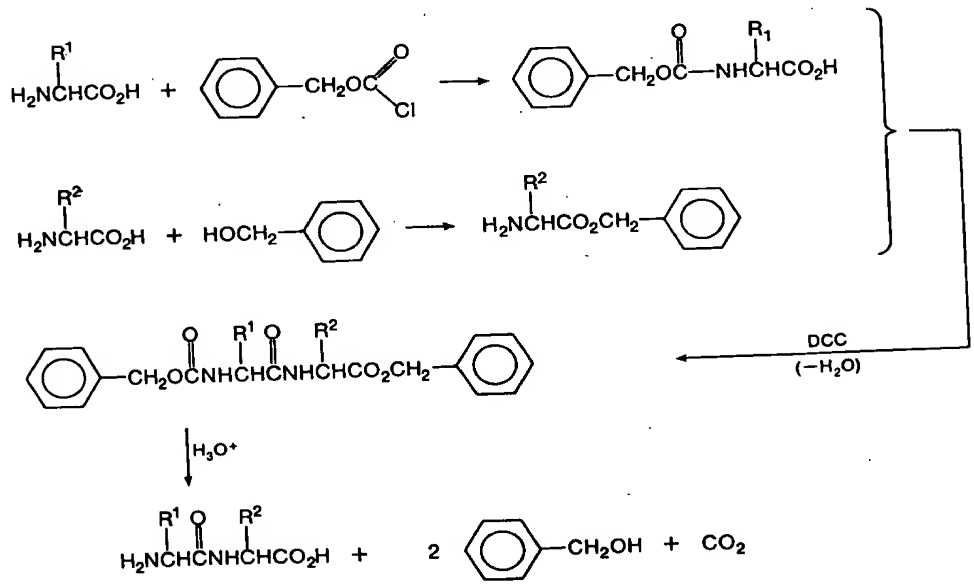



**Fig. 39.9.** Use of "protecting" groups in the synthesis of a dipeptide.